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Early markers of myocardial injury: cTnI is enough ☆

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ABSTRACT

Background: We compared the early diagnostic and prognostic performance of a highly sensitive cardiac troponin I (cTnI) assay with heart-type fatty acid binding protein (H-FABP), in the early hours of acute coronary syndrome.
Methods: Serum samples of 293 patients were studied using the Abbott Architect cTnI assay and the H-FABP assay. Special attention was paid to the diagnostic and prognostic value of admission blood samples taken <24 h after symptom onset. The prognostic endpoint was total mortality and reinfarction at 6 months.
Results: To detect forthcoming myocardial injury, admission samples gave receiver operating curve (ROC) areas (AUC) of 0.908 for cTnI and 0.855 for H-FABP ($p=0.068$) when the delay from symptom onset was <6 h (60.4% of all patients). When the delay was 6–24 h, the corresponding AUC values were 0.995 for cTnI and 0.849 for H-FABP ($p=0.002$). In multivariate analysis cTnI but not H-FABP predicted adverse events in all 293 patients (RR 3.02, 95% CI 1.62–5.63) and in those with delays <6 h (RR 2.92, 95% CI 1.47–5.81).
Conclusion: In the era of highly sensitive cTnI assays, H-FABP appears to give no additional information even in patients who present within the first 6 h after acute MI.

1. Introduction

Since the redefinition of the diagnostic criteria of myocardial infarction (MI) in 2000, the cardiac troponins (cTns) have been regarded as the preferred biomarkers in the diagnosis of MI [1]. The new universal redefinition of MI strongly prefers cTn as a marker of choice in the diagnosis of MI [2]. The highly specific cardiac troponins also have prognostic value, and they have been given a central therapy-driving role in the management of acute coronary syndromes (ACSs) [3].

It is widely known that measurable cTn levels only appear in the bloodstream 3–6 h after the cessation of regional coronary blood flow, e.g. initiation of the MI process [4]. For early identification of MI, there has been an option to use a rapidly appearing biomarker, e.g. myoglobin. Even in that case, cTn, a more specific biomarker, is recommended for retrospective confirmation of the early diagnosis [1,5]. The latest guidelines recommend that blood samples should be taken at the time of hospital admission, 6–9 h thereafter and again at 12–24 h if the earlier samples are negative for cTn and the clinical suspicion of ACS is high [2].

Since their introduction the cardiac troponin assays have been remarkably improved to allow more specific and especially more sensitive detection of myocardial necrosis [5–9]. In this paper we set out to investigate the diagnostic as well as prognostic performance of the novel, highly sensitive Abbott cTnI assay [9,10] and to compare it to the heart-type fatty acid binding protein (H-FABP), another suggested early biomarker of myocardial necrosis [11]. In ACS patients with delays up to 72 h, O'Donoghue et al. have recently demonstrated that H-FABP might have a prognostic value independent of other established clinical risk predictors and biomarkers including cTnI [12]. In another recent study, Kilcullen et al. have demonstrated similar results among ACS patients with delays of 12–24 h [13]. The need to identify high risk acute coronary syndrome patients with proper troponin assays for early treatment has also been emphasized recently [14]. Therefore, in our study special attention was paid to the diagnostic and prognostic value of the admission sample and to the impact of the recorded delay from symptom onset to presentation.

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2. Methods

2.1. Subjects and design

The original study population consisted of 531 consecutive patients who were admitted to the emergency room (ER) of the Turku University Hospital between May 2000 and July 2001 for evaluation of chest pain or equivalent symptoms suggesting myocardial ischemia as previously described [7]. For the purposes of this work we excluded patients who reported an uncertain or more than 24 hour delay from symptom onset to admission. Twenty-seven patients were also excluded because of incomplete cardiac injury marker results. The final study population comprised 293 patients (181 males, 112 females). After emergency room evaluation, 213 patients were hospitalized and 80 were discharged. All patients were diagnosed and treated according to local routine clinical protocols. All patients gave written informed consent and the local ethics committee approved the study protocol.

During patient recruitment in the ER, special attention was paid to recording the delay from symptom onset to hospital admission. Moreover, all hospitalized patients were interviewed for the onset of symptoms by the investigators. Coronary risk factors and previous medical history were systematically recorded. Killip class evaluation was performed in the emergency room and thereafter on a daily basis.

Blood samples and ECG were obtained at the time of enrollment, and in the case of hospitalized patients, 6–12 and 24 h thereafter. The Abbott cTnI was measured retrospectively using frozen (−70 °C) serum samples at the Department of Clinical Chemistry, Meilahti Hospital Laboratory, Helsinki, Finland. H-FABP levels were measured off-line using frozen (−70 °C) EDTA plasma samples at the Department of Biotechnology, University of Turku. These results were not made available to the physicians who were responsible for the patients' care during the study.

2.2. Cardiac injury markers

cTnI levels were measured with the Architect STAT Troponin I assay (Abbott Diagnostics Division, Abbott Park, IL). The assay has a minimum detectable concentration (MDC) of ≤0.01 μg/L and the cut-off level (the 99th percentile value of a reference population) for positivity is 0.032 μg/L [9]. In our precision study, CVs were 5.0% at 0.1 μg/L, 3.7% at 0.6 μg/L and 2.7% at 16.0 μg/L.

H-FABP was measured with a research immunoassay, which is based on the all-in-one dry chemistry concept. The H-FABP assay is a noncompetitive one-step immunofluorometric sandwich assay, which uses a combination of two monoclonal H-FABP antibodies and has a MDC of 0.6 μg/L with a linear range up to 250 μg/L [15]. The upper 99th percentile value of a healthy reference population (n=115) is 10.4 μg/L which was used as the cut-off for MI. The samples were analysed with the Innotrac Aio! Immunoanalyzer (Innotrac Diagnostics Oy, Turku, Finland).

2.3. ECG

The 12-lead admission ECG was retrospectively and manually coded by the third author (PP). First, patients with LBBB or undiagnostic/missing ECGs were identified. ST-segment elevation ≥0.1 mV (except V1-3≥0.2 mV) at J-point in two continuous leads was classified as ST elevation. Ischemic ST-segment depression ≥0.05 mV in at least two continuous leads was coded as having ST depression. If none of the previous criteria was fulfilled then the T-wave was measured. T-inversion was coded if it was present in ≥2 continuous leads. If none of these criteria was fulfilled, the ECG was coded as having no ischemic changes.

Table 1
Clinical baseline data of the study cohort

Age (years)	67.1 (68.1)
Sex	
Male	181 (62)
Female	112 (38)
Hypertension	128 (44)
Coronary artery disease	129 (44)
Previous MI	90 (31)
Previous coronary bypass	36 (12)
Previous PCI	28 (10)
Congestive heart failure	30 (10)
Hypercholesterolemia	171 (58)
Diabetes	51 (17)
Smoking status	
Current smoking	55 (19)
Former smoker	95 (32)
Revascularization (PCI or CABG)	28 (10)
Killip class ≥2	81 (28)
ECG changes on admission	
ST elevation	56 (19)
ST depression	47 (16)
T-wave inversion	17 (6)
LBBB	10 (3)
Missing/undiagnostic	4 (1)
Normal	159 (54)
cTnI positive (0–24 h)	135 (46)
H-FABP positive (0–24 h)	143 (49)

Age is mean (median). Other values are number (percent).

Table 2
Diagnostic performance of admission cTnI and H-FABP according to delay from symptom onset to admission blood sampling

Delay (h)	N	Sensitivity (%)	Specificity (%)	PPV	NPV	AUC
cTnI						
0–24	293	78.5	100	1.00	0.84	0.929
0–6	177	71.7	100	1.00	0.736	0.908
0–3	92	60.7	100	1.00	0.564	0.913
3–6	85	89.5	100	1.00	0.922	0.956
6–24	116	97.2	100	1.00	0.99	0.995
H-FABP						
0–24	293	68.1	89.2	0.84	0.77	0.851
0–6	177	67.7	89.7	0.893	0.686	0.855
0–3	92	60.7	90.3	0.925	0.538	0.842
3–6	85	78.9	89.4	0.857	0.840	0.898
6–24	116	69.4	88.8	0.74	0.87	0.849

2.4. Definitions and endpoints

Hospital records of all patients were retrospectively reviewed by the first and second authors (TI and JL). Patients were diagnosed using all the clinically available data, including serial ECGs. Occasional discrepancies were settled by mutual consensus. Acute coronary events were classified according to the redefined MI criteria: MI was diagnosed if the Abbott cTnI assay exceeded the cut-off value during the observational period up to 24 h and if no other known clinical cause than coronary artery disease explained the cTnI elevation [2]. Of the 293 patients, 123 were diagnosed with MI and 12 with other causes for troponin positivity (9 other cardiac and 3 miscellaneous reasons). For the purposes of this study, these 135 cTnI positive patients were grouped together and considered myocardial injury marker positive.

Follow-up data were collected from patient charts and all patients were contacted 6 months after study enrollment. The study endpoint was a combination of total mortality and myocardial reinfarction during 6 months follow-up. The mortality data including death certificates were collected from Statistics Finland.

2.5. Statistical analysis

The diagnostic performance of the different assays was compared by calculating the receiver operating characteristic (ROC) curves and area under the curve (AUC) values. The AUCs were compared with a nonparametric test for correlated data [16]. To evaluate the independent prognostic utility of cardiac injury biomarkers, a Cox proportional hazard model with stepwise selection of variables was created that included the following variables: age as continuous variable, gender, diabetes mellitus, history of hypercholesterolemia, history of hypertension, current smoking, previous MI, previous revascularization, Killip class ≥2 on admission, ST elevation on admission, ST depression on admission, H-FABP≥ 10.4 μg/L on admission and cTnI ≥0.032 μg/L. The statistical analyses were performed with SAS software (ver. 8.1; SAS Institute, Cary, NC) or with Statexact (Cytel Software corporations, Cambridge, MA). P-values <0.05 were considered statistically significant. In multiple comparisons, the Bonferroni correction was used.

3. Results

The baseline data are shown in Table 1. The median delay from symptom onset to admission blood sampling was 4.7 h (95% CI 4.1–5.4 h). The corresponding figures among patients with only cTnI or H-FABP positive on admission were 4.2 h (95% CI 3.5–4.9 h) and 4.1 h (95% CI 3.2–4.8 h), respectively.

3.1. 24 h cumulative biomarker positivity

Of the 56 ST elevation patients, 53 (94.6%) developed cTnI and H-FABP positivity within 24 h. In the ST depression group 33/47 (70.2%) became cTnI positive and 30/47 (63.8%) H-FABP positive, respectively (p=0.66). In patients without ST changes, the percentages were remarkably lower: 49/190 (25.8%) for cTnI and 60/190 (31.6%) (p=0.26) for H-FABP within the first 24 h. According to cumulative 24 hour cTnI positivity, a total of 135 patients (46.1%) developed myocardial injury.